IN THE UNITED STATES DISTRICT COURT FOR THE MIDDLE DISTRICT OF TENNESSEE NASHVILLE DIVISION

RUTH SMITH, Individually and as Widow for the Use and Benefit of Herself and the Next of Kin of RICHARD SMITH, Deceased,	)	**Case #: 3:05-00444**
	)	**Judge Trauger**
Plaintiff,	)	
-against-	)	
PFIZER INC., PARKE-DAVIS, a division of Warner-Lambert Company and Warner-Lambert Company LLC, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY LLC and JOHN DOE(S) 1-10,	)	
Defendants.	)	

PLAINTIFF'S MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTION *IN LIMINE* TO EXCLUDE ANECDOTAL ADVERSE EVENT REPORTS

INTRODUCTION

Plaintiff Ruth Smith, as the Widow for the use and benefit of herself and the next of kin of Richard Smith, deceased, by and through here attorneys, respectfully requests that the Court deny in its entirety Defendants' motion *in limine* to preclude Plaintiff from presenting anecdotal adverse event reports, (hereinafter "AER"), with respect to Neurontin. When Judge Patti B. Saris denied Defendants' motion to exclude Products Liability Plaintiffs' experts' testimony on general causation, and decided that the experts' testimony is reliable, she effectively determined that AERs, one of the criteria analyzed and relied upon by Plaintiffs' experts, is reliable. *In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 156, 157, 158 (D. Mass. 2009). This evidence is highly relevant, in accordance with Fed. R. Evid. 401, and is admissible under Fed. R. Evid. 402, as it is being offered on the issues of Defendants' notice and

knowledge. As such, the evidence is not hearsay because Plaintiff is not introducing the evidence for the truth of the matters contained therein. Further, the probative value of such evidence substantially outweighs the risk of confusing, misleading or inflaming the jury, or wasting judicial resources. Finally, introduction of the anecdotal adverse event reports, while harmful to Defendants' interest, would not be unfairly prejudicial under Fed. R. Evid. 403.

ARGUMENT

POINT I

EVIDENCE OF ADVERSE EVENTS PERTAINING TO NEURONTIN ARE HIGHLY RELEVANT AND HAVE PROBATIVE VALUE THAT FAR OUTWEIGH THEIR PREJUDICIAL VALUE

There is no question that manufacturers of potentially dangerous drugs are held to a high degree of care. As a general rule, a manufacturer has a duty to warn the ultimate user of the foreseeable risks of its product. *Richardson v. Miller*, 44 S.W.3d 1, 10 (Tenn. Ct. App. 2000). As such, prescription drugs marketed in the United States must first be approved by the Food and Drug Administration, ("FDA"). To market a brand new product, a drug company must submit a "new drug application", ("NDA"), to the FDA. *See* 21 U.S.C. § 355(a), (b). "The labeling [for the new drug] must include information necessary for the safe and effective use of the drug, such as dosage and methods of administration, as well as warnings, precautions, indications and contraindications, drug abuse and dependence, and adverse reactions." 44 S.W.3d at 11.

The Food, Drug and Cosmetic Act expressly requires a drug manufacturer to immediately inform the public of newly discovered dangers. *See* 44 Fed. Reg. 37,447 (1979). Therefore, once a drug is marketed, Defendants have an ongoing duty to "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to the FDA." 21 C.F.R. § 314.80(b). As part of this statutory pharmaceutical post-marketing

surveillance, the drug seller has a duty to monitor all information from the field about adverse reactions, monitor adverse interactions with other drugs and identify groups of consumers at special risk who would benefit from a special warning or medical monitoring. *Wyeth v. Levine*, ___ U.S. ___, 129 S. Ct. 1187, 173 L. Ed. 2d 51 (March 4, 2009).

Accordingly, the FDA requires a prescription manufacturer to issue AERs when information about adverse events reported by patients taking a particular prescription drug is received. 21 C.F.R. § 314.80(c); *see In Re: Baycol Prods. Litig.*, 532 F. Supp. 2d 1029 (D. Minn. 2007). Additionally, the FDA has indicated its recommendation that drug companies take proactive steps towards (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development." *See* *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005), attached as Exhibit A to Declaration of Kenneth B. Fromson, Esq., submitted herewith.

Reported adverse events are a signal to a drug manufacturer of safety problems with a particular drug. Notwithstanding the geographic location of an adverse event, it serves to establish defendants' notice of the signal. If the signal becomes loud enough, it is incumbent upon the defendants to take action in the form of (a) reporting to regulatory authorities, and (b) advising patients and doctors. The scope and nature of the signal is evidence of a defect in the drug's design. Common sense dictates that this information is relevant and admissible.

Here, Defendants' actual knowledge that their product was detrimental is an important component of Plaintiff's negligence, fraudulent concealment and failure to warn claims. *See, e.g., Hermes v. Pfizer Inc.*, 848 F.2d 66, 68 (5th Cir. 1988); *Golod v. Hoffman-La Roche*, 964 F. Supp. 841, 855 (S.D.N.Y. 1997) (both cases recognizing that adverse events, particularly recurring ones, may trigger a duty to warn). The AERs indicate that Defendants had knowledge

that there was an increased risk of suicide in patients taking Neurontin. It is essential that Plaintiff present this evidence of what the Defendants' course of conduct was and their conscious failure to take appropriate action and steps to inform the public and regulatory authorities of pertinent safety information about Neurontin.

If the signal for a particular adverse event becomes disproportionately louder than the signals of other events associated with the same drug or disproportionately louder than those of other drugs within the same class of drugs, then Defendants are obligated to take action. *Hermes v. Pfizer, Inc.*, 848 F.2d 66; *Golod v. Hoffman-La Roche,* 964 F. Supp. 841 (both recognizing adverse events). The scope and nature of the signal is evidence that the drug may have been defectively designed or manufactured, or lacked adequate warnings to users who should not have been taking the drug, or who should have been monitored more closely by physicians.

Defendants' argument that AERs are inadmissible because they are irrelevant to any issue in this case is without merit. AERs are regularly relied upon by experts and clearly admissible under the Federal Rules of Evidence. *See Bocanegra v. Vicmar Servs., Inc.*, 320 F.3d 581 (5th Cir. 2003) (citing *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993)). To be admissible, evidence must be relevant. Fed. R. Evid. 401. Relevant evidence is defined as evidence which may tend to prove or disprove a material fact that is of consequence to the determination of the action.. Fed. R. Evid. 401. Significantly, a movant *in limine* has the burden of establishing that the evidence sought to be excluded on relevancy grounds is not relevant to any issue in the case. *See Chrysler Credit Corp. v. Whitney Nat'l Bank*, 824 F. Supp. 587, 599 (E.D. La. 1993). Clearly, Defendants have not met their burden.

First, it is evident that the AERs herein are relevant. In her May 5, 2009 Memorandum and Order, Judge Patti B. Saris noted that Plaintiff's experts relied upon Periodic Safety Update

Reports, which included cases of adverse events. She acknowledged that Plaintiff's expert, Dr. Cheryl Blume, opined that Neurontin can be associated with suicide-related behavior. *In re Neurontin*, 612 F. Supp. 2d at 156, 157. Clearly, in denying Defendants' motion to exclude Plaintiff's experts' testimony on general causation, Judge Saris concluded that the causation testimony was reliable under *Daubert* and she determined that Plaintiff demonstrated that a relationship between Neurontin and suicidality is biologically plausible. *Id.* at 158.

Second, Defendants argue that adverse event reports cannot be used to establish causation. Although Plaintiff has never specifically stated that, the post marketing AERs do establish a causal relationship:

> While these events do not prove that Neurontin causes suicidal behavior, they do demonstrate, in conjunction with the vast numbers of post-marketing events, that Neurontin can be associated with suicide-related behavior.

Id. at 157 (citing expert report of Dr. Cheryl Blume).

> Further, FDA employees have published opinions to the contrary where they state that AERs can be used to establish causality, although this is a rare occurrence:
>
> In fact, it has been suggested that a temporal relationship between medical product and adverse event, coupled with positive de-challenge and re-challenge, occasionally make isolated reports conclusive as to a product-event association. Biological plausibility and reasonable strength of association aid in deeming any association as causal.

Brian L Strom, *Pharmacoepidemiology* (Wiley, 2005), p. 152.

The FDA clearly uses AERs in the context of establishing a causal relationship. In the FDA's carefully considered Guidance for Industry, Fromson Decl., Ex. A, it plainly indicates that "[a]fter the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event." Ex. A at 17. Included is information from spontaneous reports. Therefore, as Judge Saris has already concluded, adverse event information is probative on the question of causality.

The purpose of a motion *in limine* is to allow the trial court to rule in advance of trial on the admissibility and relevance of certain forecasted evidence. *See Sanders v. Ritz-Carlton Hotel Co., LLC.*, No. 05 Civ. 6385 (PKL), 2008 U.S. Dist. LEXIS 68371 (S.D.N.Y. Sep. 9, 2008). However, the documentary evidence supporting the motion must be authenticated for consideration of its admissibility. Under Fed. R. Evid. 901(a), documents must be properly authenticated as a condition precedent to their admissibility "by evidence sufficient to support a finding that the matter in question is what its proponent claims." *United States v. Siddiqui*, 235 F.3d 1318, 1322 (11th Cir. 2000).

A document may be authenticated by "appearance, contents, substance, internal patterns, or other distinctive characteristics, taken in conjunction with circumstances." Fed. R. Evid. 901 (b)(4). A district court has discretion to determine authenticity. *Siddiqui*, 235 F.3d at 1322. The document in question (Defs. Ex. A, Docket No. 111-1) lacks any markings from the FDA and does not even come from the e-mail account of Dr. Dobbs, which is listed on the Health and Human Services Website as "donald.dobbs@fda.hhs.gov." Furthermore, Dr. Dobbs' mailing address and phone numbers are not provided at the bottom of the e-mail, as is customary for other e-mails from the FDA. As such, it is unclear who at the FDA, if anyone, actually sent the e-mail in question. This is most troubling considering that Defendants are attempting to use this e-mail as representation of the official position of the FDA. When asked about the e-mail at his deposition on December 5, 2008, Dr. Ruggieri stated:

Q. Did you receive this e-mail through your home computer?

A. Yes.

Q. Do you still have the e-mail on your home computer?

A. I don't think I do.

Fromson Decl., Ex. B at 277:22-278:2.

Dr. Ruggieri has never produced the e-mail with routing information, which could settle the question of its authenticity. Defendants have been well aware of Plaintiff's questions concerning the authenticity of this document, yet have failed to provide any documentation that would prove its authenticity. They could simply have obtained a "red ribboned" version of the e-mail from the FDA to validate its authenticity but failed to do so, which renders the e-mail's validity suspect at best.

Aside from its authenticity, the document is inadmissible hearsay. The document purports to set forth the FDA's position regarding the use and significance of AERs in the context of suicidality. According to Defendants, Dr. Dobbs allegedly provides the position of the FDA. It is unclear that Dr. Dobbs is authorized to provide official policy determinations of the FDA. Additionally, since Defendants are putting forth this e-mail to prove that the FDA does not believe that AERs can be used to determine causality, the document is classic hearsay. The e-mail does not fall under any of the hearsay exceptions as it does not satisfy the requirements of Fed. R. Evid. 803(6) or 803(8). It is therefore inadmissible hearsay and not relevant to any issue herein, especially the FDA's position on whether information in the AERs can cause increased suicidal thoughts or behavior in patients taking antiepileptic drugs.

In further support of their position that AERs cannot be used to determine causality, Defendants reference a letter that in fact supports Plaintiff's position. Defendants cite to a letter to Andrew Fromson from Russell Katz where Dr. Katz writes: "in the absence of an appropriate control group, it will be difficult, if not impossible, to assess the role of any other factors that might explain these events, such as concomitant medications." Defs. Ex. B, Docket No. 111-2. On its face, this sentence does not say it is impossible to draw such a conclusion, only difficult.

The above referenced e-mail and letter are inconsistent with the opinions of the FDA and FDA staff as discussed in Strom's *Pharmacoepidemiology* and the *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005). Fromson Decl., Ex. A. Therefore, even if the Court accepts the Dobbs' e-mail as authentic, there is a conflict between the documents, and therefore the Court should let the jury decide whether the FDA utilizes adverse events to establish a causal relationship.

Defendants also argue that the AERs are not relevant to the issue of notice because there would have to be a "substantial similarity" between the AERs and the specific facts of this case. Defs. Mem., Docket No. 110 at 7-8. The requirement of similarity of circumstances is relaxed where evidence, such as AERs or clinical investigative reports, is offered to show that a defendant had notice of a danger rather than where the prior incidents are directed at proving actual negligence. *Kehm v. Procter & Gamble Mfg. Co.*, 724 F.2d 613, 626 (8th Cir. 1983) (court explained that it was up to the jury to decide what weight to give complaints from customers). The FDA itself in the approved 2009 Medication Guide for Antiepileptic Drugs lists several adverse events which may be related to suicidal behavior. Fromson Decl., Ex. C at 9. Such a determination by the FDA clearly indicates that the FDA considers several different events to be related to the question of suicidality. Further, "[u]nder Fed. R. Evid. 401, evidence of similar occurrences 'might be relevant to the defendant's notice, magnitude of the danger involved, the defendant's ability to correct a known defect, the lack of safety for intended uses, [or] the standard of care, and causation.'" *Ramos v. Liberty Mut. Ins. Co.*, 615 F.2d 334, 338-39 (5th Cir. 1980). One facet of Plaintiff's claims is that there was a spectrum of adverse event reports that should have been reviewed by Defendants as part of their regulatory duties. The FDA's letter to

the sponsors supports Plaintiff's position that there are many different events that are relevant to the question of suicidality and thus Defendants' argument must fail. Fromson Decl., Ex. C.

Defendants further argue that AERs are inadmissible under Fed. R. Evid 403. Rule 402 provides that relevant evidence is admissible. Further, the Federal Rules of Evidence provide that "relevant evidence may be excluded if its probative value is substantially outweighed by the risk of (a) undue prejudice, confusion of issues, or misleading the jury or (b) undue delay, waste of time, or needless presentation of cumulative evidence." Fed. R. Evid. 403 (emphasis added).

Relevant evidence is inherently prejudicial; it is only *unfair* prejudice that *substantially* outweighs probative value which permits exclusion of relevant matter under Fed. R. Evid. 403 .(emphasis added). Notably, the exclusion of relevant evidence under Rule 403 should occur only sparingly. *See United States v. Pace*, 10 F.3d 1106 (5th Cir. 1993).

AERs are regularly relied upon by experts and clearly admissible under the Federal Rules of Evidence. Plaintiff will utilize the AERs to prove that Defendants had notice of the risk of suicidal behavior. Furthermore, the growing number of events combined with the ever increasing off-label usage of Neurontin, and Defendants' failure to demonstrate the safety and efficacy in those populations demonstrates negligence and recklessness, both part of Plaintiff's claims. The introduction of the AERs will be used to demonstrate that the suicidal risk associated with Neurontin was known and available to Defendants, and that earlier warnings of this danger could have been placed on the label. This evidence is highly probative of Plaintiff's negligence and failure to warn claims and would be easily understood by jurors.

The introduction of AERs to establish notice and knowledge will not confuse and mislead the jury. Contrary to Defendants' assertion that the AERs will infer causation by a jury, a limiting instruction can remedy this issue. *See Maudlin v. Upjohn Co.*, 697 F.2d 644, 648 (5th

Cir. 1983) (explaining how a limiting instruction by the court as to the use of AERs in determining notice, prevented possible jury confusion and/or prejudice with regard to AERs which report injuries other than the one at issue). Further, the time and testimony that would be necessary for Defendants to deny notice of voluminous AERs would be minimal, at best, and not meet the level of undue delay under Fed. R. Evid. 403. The fact that Defendants received and kept records of AERs relating to the ingestion of Neurontin goes directly to the issue of awareness of the dangerous propensities of its prescription drug.

Since AERs are relevant, and their probative value substantially outweighs the risk of confusing, misleading or inflaming the jury, or wasting judicial resources, said relevant evidence is admissible and should not be excluded.

POINT II

EVIDENCE OF ADVERSE EVENT REPORTS IS NOT HEARSAY

AERs are admissible over hearsay objections; they do not fall within the definition of hearsay under Fed. R. Evid. 801 to the extent that they are not being offered to prove the truth of the matter asserted. Further, the FDA's maintenance of an AER database is mandated by 21 C.F.R. § 314.80 *et. seq*., and therefore excepted from the hearsay exclusionary rule pursuant to Fed. R. Evid. 803(6) and 803(8). Defendants contend that they are improper proof of causation, irrelevant and hearsay. But they are neither hearsay nor proof of causation at all. They are not hearsay because they are not offered for the truth of the matter asserted. The point of the AERs is to demonstrate the state of Defendants' knowledge and to show their negligent failure to investigate and evaluate further; the evidence are not being offered to demonstrate causation.

The mere fact that AERs are not official records is immaterial. Several district courts have admitted "informal" FDA statements. *See, e.g., Kennedy v. Baxter Healthcare Corp.,* 348

F.3d 1073, 1075 (8th Cir. 2003) *per curiam* (no abuse of discretion in admitting "informal FDA pronouncements" because they "were probative of whether Baxter acted reasonably in designing, labeling, and selling its rubber gloves"); *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1046, 1050 (S.D. Ill. 2001) (court acknowledged that a large amount of case report showing a temporal proximity between a very specific drug and a very specific adverse event might be enough to make a general causation conclusion sufficiently reliable).

The anecdotal AERs will be introduced for the purpose of demonstrating that Defendants had notice, a key element in failure to warn and fraudulent concealment claims, and knowledge of the serious hazards reasonably associated with Neurontin, and of Defendants' reaction to that notice and knowledge. *See, e.g., Seroquel Prods. Liab. Litig.,* 601 F. Supp. 2d 1313, 1316 (M.D. Fla. 2009).

Additionally, AERs are admissible as an exception to the hearsay rule for statements made for purposes of medical diagnosis or treatment, because an important purpose of the AER is to identify whether the cause of an adverse reaction is indeed due to the ingestion of that specific drug. Fed. R. Evid. 803(4).

The AERs are probative of Defendants' notice and knowledge of information that may lead a reasonable juror to believe that Defendants misrepresented, or omitted, that information or failed to meet the standard of care relative to warning about the drug's risks. *Id.* Since Defendants have failed to demonstrate that AERs are hearsay, their argument for exclusion on this basis must fail.

CONCLUSION

For the foregoing reasons, Defendants' Motion *in Limine* should be denied.

Dated: April 27, 2010

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this the 27th day of April, 2010, I electronically filed the foregoing document with the Clerk of the Court, United States District Court for the Middle District of Tennessee, using the CM/ECF system. True and correct copies of the foregoing documents are being served via the Court's CM/ECF system on the following:

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